PARTICULARITIES OF THE TRANSGENDER BRAIN

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ABSTRACT

As the list of possible causes for transgender identity continues to develop, it has become clearer and clearer that it is not a conscious choice. In this context, earlier diagnosis and a more complex understanding of the phenomenon could help improve the quality of life for transgender people, as well as lead to more informed decisions regarding treatment.

More studies show evidence that transgender individuals display certain structural and functional brain characteristics of their desired gender and may have gone through processes of atypical neuronal sexual differentiation. The brains of transgender individuals do not seem completely feminized or masculinized, research rather pointing towards a process of selective feminization or masculinization of the certain brain structures that are sexually dimorphic in control subjects.

The aim of this article is to give an overview of the structural and functional neurobiological particularities of the transgender brain. Still, there are limitations to these studies including: inconsistent results, small sample sizes, data available for male-to-female transgender only, and the results not giving enough information about the participants' sexual orientation.

We need to know this information in order to be able to provide the best care for our transgender patients and to contribute to reducing the stigma associated to this social category.

Keywords: transgender, gender dysphoria, brain, neurobiological

INTRODUCTION

Trangenderism is a phenomenon which describes persons who don't identify with their birth assigned gender [1]. Trangenderism was found in the previous editions of the DSM as Gender Identity Disorder, but it was removed in 2013. Along with the release of DSM-5, clarifications were made regarding the phenomenon and the gender dysphoria diagnosis replaced the gender identity disorder. What led to this decision was that experts stopped seeing transgenderism as a medical disorder per se. In order to be diagnosed with gender dysphoria you would have to be trangender, but also feel a certain degree of distress as a result of it. When this distress feels overwhelming, transgender people want to transition to the desired sex through hormone replacement therapy or sex-reassignment surgery. For the diagnosis, the following two main criteria need to be met: strong incongruence between one's assigned and experienced gender that manifests itself in the desire to be of the other gender and to be treated as such, as well as clinically significant distress or impairment in functioning. A transgender man is a person who was assigned with a female gender at birth, but identifies with the male gender, while a transgender woman was born a man but identifies with the female gender. A cisgender person identifies with the sex assigned at birth.[1]

There are few epidemiological studies showing the prevalence of trangederism and the data varies from country to country. In the

DSM-5 it is reported a prevalence of 0,005% up to 0,014% for natal males and 0,002 up to 0,003% for natal females. Moreover, since not every trasngender person undergoes hormone-replacement therapy or sex-reassignment surgery, numbers might also be underestimated. Sex ratio seems to differ with age, varying from 2:1 to 4,5:1 in children, in favor of native males, reaching parity in teenagers and 1:1 up to 6,1:1 in favor of native males in adults [2]. Although many studies seem to favor native males when it comes to transgenderism sex ratio, there appears to be newer studies that show an inversion in the sex ratio. Arcelus J et al. describe the complexity of establishing the real prevalence of transgender persons because of several factors like the fact that diagnosis criteria and terminology have been changing in the last years. There are also factors regarding the subjects and the methods used like the fact that studies undertaken in "trans friendly" cities or countries, like Holland, might show a prevalence that is not relevant for other cities or countries, since transgender persons tend to go and live there. However, the prevalence has risen in the last two decades, though this could partly be the result of the destigmatization process and the increase of tolerance towards them. [3]

It seems that people with gender dysphoria have more psychiatric comorbidities than the general population. A multicenter study that investigated adults seeking gender reassignment therapy in four European countries showed that up to 70% of the participants had criteria for at least one Axis 1 diagnosis, especially affective and anxiety disorders with no differences between genders. Regarding axis 2 disorders, 15% were diagnosed with personality disorders (schizoid,avoidant and borderline personality disorders). Substance use, eating disorders, and psychotic disorders were less prevalent. For all the countries included it looked like people with gender dysphoria had higher rates of psychiatric disorders, for both genders [4]. In terms of suicidality, The National Transgender Discrimination Survey showed that 41% (out of 6,450) of respondents reported attempting suicide compared to 1.6% of the general population, with rates rising for those who lost a job due to bias (55%), were harassed/bullied in school (51%), had low household income, or were the victims of physical assault (61%) or sexual assault (64%). Summerizing research findings on suicidality in LGBT persons, Terada et al reported that being transgender is a risk factor itself for suicidal behavior and not related to the psychiatric comorbidities [5].

During the intrauterine period, the sexual development of the brain takes a masculine path under the influence of testosterone and a feminine path in the absence of it. Interestingly, the maturization of the genitals takes place in the first two months of the pregnancy, while the sexual development of the brain only begins in the second part of it. This means that the two processes could develop in opposite directions under the influence of different factors, which may lead to transgenderism [6].

NEUROANATOMY PARTICULARITIES

Despite the fact that a neurobiological marker for being transgender has not yet been found, there are studies trying to establish if the sexually dimorphic brain structures in transgender persons are more similar to those in their birth attributed gender or to the one they identify with. Structural and functional brain particularities have been the subject of both anatomical, postmortem studies and in vivo neuroimaging ones.

WHITE MATTER

Studies analyzing corpus callossum in transgender persons often came up with contradictory results [7].While former studies looking at the corpus callossum found no difference in its structure depending on

gender, a study from Yokota et al. (2005) not only claimed they found a way to tell the difference between males and females using a midsagital plane of the structure, but they also observed that their measures in transgender subjects reflected their desired gender, not the biological assigned one, but their results haven't been replicated since then [8].

Other studies, using diffusion tensor imaging (DTI), investigated white matter patterns in sexually dimorphic fiber tracts. Rametti et al. (2011) analyzed white matter fibers in both male-to-female and female-to-male transgenders, observing a microstructure more similar to the gender identity for the female to male subjects [9]. For the male-to-female cohort, study showed an intermediate phenotype of the white matter microstructure, somewhere in between the female and the male group control, thus suggesting that in the differentiation process, some of the fibers do not complete the masculinization process [10].

Later on, Kranz et al. (2014) undertook a study to investigate the white matter microstructure in male-to-female, female-to-male transgender persons, female and male group controls using DTI. They included 89 participants and they correlated the measures with their birth gender, their identity gender, their hormone levels and their sexual orientation. They found the highest mean diffusivity values in female controls, followed by female-to-males, male controls and male-to-female transgenders [11] This study contradicts the previous ones in terms of parameters tested and exact order of the findings,but they all seem to agree on the idea that female-to-male and male-to-female transgender individuals fall halfway between the male and female group controls in terms of white matter microstructure. [12]

GREY MATTER

Past research investigating sexually dimorphic areas of the grey matter has been consistent about two structures: the central subdivision of the bed nucleus of the stria terminalis (BSTc) and the third interstitial nucleus of the anterior hypothalamus (INAH3). [13]

In a study from 2009, Alicia Garcia-Falgueras and Dick F. Swaab looked into the differences of the hypothalamic uncinate nucleus, consisting of two subnuclei, INAH3 and INAH4. Using postmortem brain material from 42 individuals (14 control males, 11 control females, 11 male-to-female transgenders, 1 female-to-male trangeder and 5 castrated subjects due to prostate cancer) they showed that INAH3 subnucleus' volume is 1.9 times larger in men than women and contains 2.3 times more neurons. Moreover, INAH3 in male-to-female individuals seemed closer to the female group control and the same was observed for the female-to-male individual. An interesting observation was that no difference in volume or neuron number was observed between pre and post menopausal women, indicating that estrogen treatment didn't have anything to do with the feminization of the INAH3 in male-to-female individuals. [14] It seems, therefore, that BSTc and INAH3 could be markers of a sex-atypical differentiation of the transgender individuals` brains.

PET AND SPECT STUDIES

In 2012, Kranz et al started to study the serotonin transporter distribution using positrone emission tomography. Knowing from previous research that there are asymmetries between sexes in the neurotransmitter's distribution, they compared the pattern in male to female transgenders, female controls and male controls. Besides many left and rightward asymmetries in nearly all brain regions independent to gender, they also found a rightward asymmetry in the male individuals, in the midcingulate cortex. This asymmetry was absent in the female control group and the male to female individuals, pointing to the idea that there is an incomplete

masculinization in the brain of male to female transgenders[15].

In a study form 2010, Nawata et al looked into the regional cerebral blood flow in individuals with gender dysphoria. Single-photon emission computed tomography (SPECT) was performed for 11 female to male subjects and a control group. They found increased regional cerebral blood flow (rCBF) in the right insula and decreased rCBF in the left anterior cingulate cortex. These areas of the brain are known to have a role in human sexual arousal induced by visual sexual stimulation and the insula is also involved in the bodily self-awareness, thus suggesting valuable information on the biological basis of gender dysphoria [16].

FUNCTIONAL NEUROIMAGING STUDIES

In functional neuroimaging studies, attention has been directed towards olfactory and voice processing activation patterns and sex-typical activation tasks such as mental rotation and language fluency.

Estratetraenol and androstadienone are steroid compounds known to activate hypothalamic networks in a sex-differentiated manner through their pheromone capability. By using these chemosignals which can be found in human secretions, Berglund et al. (2008) compared the cerebral activation patterns in 12 nonhomosexual male-to-female transgender individuals to 12 heterosexual men and women. The results of their study showed an atypical pattern of hypothalamic activation in the transgender group, more similar that of the women control group, while differing significantly from the male control group's.

While it does not provide conclusions on the aetiology of transgenderism, this study contributes to the evidence that shows a sex atypical activation pattern in certain regions of transgenders' brains [17].

Burke et al. (2014) replicated the study on a cohort of male and female pre-pubertal children and adolescents and individuals with gender dysphoria. During olfactory stimulation with androstadienone, hypothalamic responses were already present and sex dimorphic in pre-pubertal children from the control group. In contrast, pre-pubertal girls with gender dysphoria expressed neither a masculine, nor a feminine activation pattern, while pre-pubertal boys showed an activation pattern consistent with their birth assigned gender. Adolescents with gender dysphoria, on the other hand, expressed atypical hypothalamic activation, similar to the identity gender, once again suggesting they may have gone through a atypical pathway in the sexual differentiation of the brain [18].

Gender dependent differences in responding to sexual visual stimulation have already been established. Stoleru et al, in a meta-analysis on sexual arousal in healthy men and women, found that in heterosexual men, the sites of cerebral activation that are most often mentioned in literature are the lateral occipitotemporal, inferotemporal, parietal, orbitofrontal, medial prefrontal, insular, anterior cingulate, and frontal premotor cortices and the amygdalas, claustrum, hypothalamus, caudate nucleus, thalami, cerebellum, and substantia nigra in the subcortical regions. The amygdalas and thalami were shown to be less activated in women during sexual visual stimulation. [19]

Considering these gender-specific results during erotic stimulation, Gizewski et al. (2009) compared the cerebral activation pattern in 12 male to female individuals to 12 heterosexual females and 12 heterosexual men viewing erotic movies. The study revealed a cerebral processing of the images similar to the desired gender in the male to female individuals[20], even though a certain conclusion cannot be drawn from this study, since sexual orientation in the transgender group was mixed, unlike the control group who stated to be heterosexual. [12]

Coinciding with , Gizewski et al's results, another study from 2013 found connectivity profiles of the desired gender in 21 female to male and 20 male to female individuals. [21]

The human voice is one of the human secondary sexual characteristic playing an important role in male selection. Previous studies demonstrated an opposite-sex effect, meaning that voice are better recognized by the opposite sex. Junger et al, in a fMRI study from 2014, compared the neural activation patterns in 32 male to female trasgender individuals and non-gender dysphoric men and women controls, during voice gender perception. Male to female individuals showed weaker activation than men in the right hemispheric area triangularis, insula, cuneus, bilateral lingual gyrus,calcarine gyrus and in the left parahippocampus and weaker activation than women in the medial prefrontal cortex, rostral anteriorcingulate cortex, right superior temporal gyrus, thus supporting the idea of transgenders occupying an intermediate position between men and women controls. [22]

Another direction of work in transgender care was directed towards neurocognitive functions that are supposed to be sexually dimorphic such as mental rotation and speech and language fluency. Men are known to be better at visuospatial tasks, while women outperform them in language tasks [23].

Studies have looked into these sex-sterotypical cognitive abilities in persons with gender dysphoria to see if their performance matches their biological or their desired gender. Schöning S et al investigated male to female transgender individuals, some of which prior to cross-sex hormonal treatment and compared them with non-gender dysphoric males. They had to perform a mental rotation task while undergoing functional magnetic resonance imaging. In comparison with the control male group who showed grater activation in the left parietal cortex, transgender individuals exhibited stronger activation patterns in the temporo-occipital regions of the brain. The study confirmed the hypothesis that untreated transgender individuals differ from non gender dysphoric men in their activation pattern during mental rotation tasks and also these differences seem to increase along with undergoing cross-sex hormonal treatment [24]. In another mental rotation task performing study, investigating both male-to-female and female-to-male transgender individuals under chronic hormonal treatment, Carillo et al observed that male to female individuals exhibited decreased parietal lobe activation, relative to cisgender men, but increased activation in the right orbital and dorsolateral prefrontal cortex relative to cisgender women. Female to male individuals did not exhibit any group effect differences [25].

If males are known to perform better in mental rotation tasks, women are favoured in tasks involving verbal fluency and language.

In a study evaluating verbal fluency in gender dysphoric adolescents and control boys and girls, Soleman RS et al found that cisgender boys exhibit greater activation than cisgender girls in the right Rolandic operculum. The trans girls showed better performance of female-favoured tasks, but curiously, they were better than all the other three groups. [26] This study sustains the hypothesis of a biological basis for transgenderism, even though the results should be cautiously interpreted sincer the effects did not reach statistical significance. [27]

CONCLUSIONS

Even though the true prevalence of transgenderism is hard to establish, the incidence seems to have been increasing worldwide over the last two decades. There is still a high rate of psychiatric disorders transgender people experience, especially from the anxiety and depression spectrum, while the risk of suicidality among this category of persons remains concerning. Beginning the process of transition through cross-sex hormone therapy and sex-reassignment surgery

seems to decrease the severity of the psychiatric symptoms. While the evidence for a biological etiology of transgenderism is still modest, there are studies that point towards some nerobiological underpinnings of the phenomenon. The transgender brain seems to be falling into an intermediate phenotype position, not entirely feminised or masculinised. Still, many of the research on this topic came up with mixed results because of various factors: some of the studies have low statistical power either including small number of transgender persons and cisgender control individuals or not including control groups at all. Some of the studies lack relevant data about the participants, such as sexual orientation, which definitely plays an important role in this topic.

At the moment it seems hard to draw any clear conclusions, the phenomenon being insufficiently studied, but a lot of progress has been made in the last decade and hopefully future research will help reduce the stigma associated with transgenderism.

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